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CHAPTER 1

General introduction

Head and neck squamous cell carcinoma

Squamous cell carcinoma of the mucosal lining, is the most frequent malignancy of the head and neck region, and accounts for 4% of all malignant tumors worldwide (1). The incidence increases with age, with most patients over the age of 55. More than two thirds of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced stage disease. Laryngeal carcinoma is the most frequent tumor within the head and neck in North-western Europe. In 2012 the annual incidence of laryngeal cancer in the Netherlands was 3.4 per 100,000 individuals (2).

LARYNGEAL CARCINOMA

Anatomy and Physiology

The larynx represents the junction of the upper and lower portions of the airway and essentially serves two functions: protection against aspiration and phonation. The larynx extends from the tip of the epiglottis to the lower edge of the cricoid cartilage and is divided anatomically into three parts: the supraglottis, glottis, and subglottis. The supraglottis extends from the tip of the epiglottis to the level through the paired laryngeal ventricles. Because the supraglottis is derived from the fourth branchial arch, the rich lymphatic drainage runs cranially to the upper deep jugular chains of lymph nodes (level II and III). The glottis is a small area that contains the true vocal cords and extends from the laryngeal ventricles to an imaginary plane approximately 1 cm below the true vocal cords. The subglottis extends from 1 cm below the true vocal cords to the lower edge of the cricoid cartilage. Both the glottis and subglottis have sparse lymphatic drainage, located inferiorly into the lower deep jugular nodes and paratracheal nodes (levels IV and VI). The glottic area mainly serves phonation while the supraglottic area mainly serves protection against aspiration during swallowing (3).

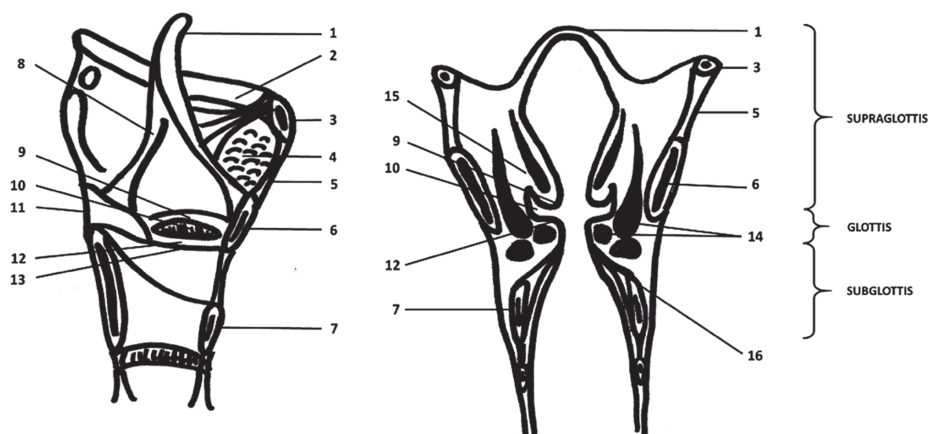


Fig 1. Sagittal (left) and coronal (right) view of the larynx. Adapted from reference 3. 1=epiglottis, 2=hyoepiglottic ligament, 3=hyoid bone, 4=preepiglottic fat, 5=thyrohyoid membrane, 6=thyroid cartilage, 7=cricoid cartilage, 8=aryepiglottic fold, 9=false vocal cord, 10=laryngeal ventricle, 11=arytenoid cartilage, 12=true vocal cord, 13=vocal ligament, 14= thyroarytenoid muscles, 15= paraglottic space, 16=conus elasticus.

Epidemiology

There are approximately 700 new patients with laryngeal carcinoma in the Netherlands per year; 200 persons die each year from this disease (4). Laryngeal cancer is more common in males than in females. The worldwide incidence varies per country and age-standardized incidence rates are highest in men in Central and Eastern Europe and Southern Europe and lowest in Eastern Asia, West Africa and Middle Africa (5,6). The variations in incidence rates both between countries and between men and women are likely related to differences in smoking behavior and to a lesser extent to differences in alcohol consumption. The combined effect of these two risk factors is estimated to account for 89% of laryngeal cancer cases (7). Smoking is the largest risk factor for the development of laryngeal cancer, with a synergistic effect of heavy alcohol consumption. Alcohol intake is also a risk factor on its own for supraglottic carcinomas. Patients are typically in their 6th decade of life when laryngeal carcinoma is diagnosed (2,8).

In most of the patients the tumor is localized in the supraglottis (epiglottis, arytenoids, aryepiglottic folds and false vocal cords), or in the glottis (true vocal cords, anterior and posterior commissures), and only 2% in the subglottis. Glottic carcinomas are often diagnosed early (60% stage I) since persistent hoarseness is an early symptom. Supraglottic carcinomas lack specific symptoms (symptoms are: increased mucus production, dysphagia, globus, dry en raw sensitization of the throat) and are therefore diagnosed in a later stage (two-third with stage III or IV) (4).

Staging

The Union of International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) have designated staging by TNM classification to define laryngeal cancer (9,10). The most common localization of distant metastases is in the lung. Further classification into prognostic groups can be made: early stage (stage I-II) and advanced stage (stage III-IV).

Primary treatment

In the treatment of laryngeal cancer preservation of function without compromising chances of cure is challenging. The larynx harbors functions of vocalization, swallowing and respiration. Preservation of an intelligible voice is an important consideration in choosing a treatment modality.

Patients with early-stage disease can very effectively be treated with single-modality larynx-sparing approaches. Small superficial cancers are successfully treated by radiation or surgery alone, including endoscopic laser excision surgery (11-14). Reviews on the outcomes of radiotherapy and laser resections suggest comparable local control and survival with similar low risks of major complications (15,16), although no randomized controlled trial is performed (17). Laser resection is an effective, single use, relatively low-cost treatment which can be repeated (18,19). Lesions that are deeper infiltrating or indistinct from non-tumorous tissue, especially those arising in the context of widespread, abnormal-appearing mucosa, seem to be more suitable for radiation therapy (20-22).

Table 1. TNM classification larynx (7th edition 2009).

<i>Supraglottis</i>	
T1	One subsite with normal mobility
T2	Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; without fixation
T3	Cord fixation, or invasion of postcricoid area, pre-epiglottic tissues or paraglottic space, or thyroid cartilage erosion
T4a	Extension through thyroid cartilage; or extension of trachea or soft tissues of neck: deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
<i>Glottis</i>	
T1	Limited to vocal cord(s) with normal mobility (a) one cord (b) both cords
T2	Extension to supraglottis or subglottis, or impaired cord mobility
T3	Cord fixation or invasion of paraglottic space or thyroid cartilage erosion
T4a	Extension through thyroid cartilage; or extension to trachea or soft tissues of neck: deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
<i>Subglottis</i>	
T1	Limited to subglottis
T2	Extension to vocal cord(s) with normal or impaired mobility
T3	Cord fixation
T4a	Extension through cricoid or thyroid cartilage; extension to trachea, deep or extrinsic muscle of tongue, strap muscles, thyroid or oesophagus
T4b	Extension to prevertebral space, mediastinal structures or carotid artery
<i>All sites</i>	
N1	Ipsilateral single lymph node metastasis ≤3 cm
N2	(a) ipsilateral single lymph node metastasis >3-6 cm (b) ipsilateral multiple lymph node metastases ≤6 cm (c) bilateral, contralateral lymph node metastases ≤6 cm
N3	lymph node metastasis >6 cm
<i>All sites</i>	
M1	Distant metastasis

Table 2. Stage grouping larynx.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T3	N0, N1	M0
IVA	T4a, T4b	N0, N1	M0
	T1, T2, T3	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

In the last decades the treatment of advanced laryngeal carcinoma has evolved. Advanced laryngeal carcinoma was historically primarily treated by surgery (laryngectomy), but more recently the trend has shifted to (chemo)radiation. Non-surgical treatment is aimed at preservation of voice, normal respiration and swallowing and reserves surgery for salvaging purpose if needed. Two clinical studies had major effects on the management of advanced laryngeal cancer. The first in 1991, found that induction chemotherapy followed by definitive radiotherapy resulted in little difference in survival compared to patients receiving total laryngectomy and postoperative radiotherapy (23). The second, in 2003, reported that concurrent chemotherapy and radiotherapy were superior to sequential chemoradiation or radiotherapy alone for achieving local and regional control when applied to stage III and IV laryngeal cancer with T2, T3, or 'limited' T4 tumors (24).

Standard fractionation radiotherapy (60-70 Gy at 1.8-2 Gy fraction doses) is the most commonly used modality for early stage cancer (25). Hyperfractionation or accelerated fractionation radiotherapy have shown a higher local control rate with more acute adverse effects, as compared to standard fractionation (26-28). Since a decade intensity-modulated radiation therapy (IMRT) has been incorporated into clinical use, a dynamic radiotherapy technique with the ability to spare vital organs, such as salivary glands, orbital tissue and the central and spinal nervous tissue (29,30).

For advanced laryngeal carcinoma the combination of radiotherapy and chemotherapy is preferred. Concurrent chemoradiotherapy with a platinum-based chemotherapy has become the standard of care (24). The most often used chemoradiation scheme in our center consists of 7 weeks radiotherapy (fraction dose 2 Gy, 5x/week) combined with cisplatin (3 courses of 100 mg/m² in week 1, 4 and 7 of radiotherapy).

Although many larynges have been saved by chemoradiation, increasing concern arises about late toxicity and decreased survival (31,32), which might be (partially) attributed to inappropriate patient selection for chemoradiation (33,34). Especially patients with the most advanced stage primary laryngeal carcinoma (stage IV with cartilage invasion or involvement of the soft tissues of the neck) and expected poor tolerance of treatment seem to have better survival chances with primary laryngectomy (34-37).

Local recurrences

A local recurrence is defined according to clinical criteria as the occurrence of carcinoma within three years after and localized less than two cm from the first tumor. Tumors more than two cm away from or after more than three years after the primary tumor are referred to as a second primary tumor (38).

When cancer cells have remained in the patient this can be designated residual disease and outgrowth of these cells is a possible cause of local recurrent cancer. Sometimes these cells can only be detected by sensitive molecular methods and are referred to as 'minimal residual cancer' (39). Also, fields of genetically altered cells surrounding and in the neighborhood of the tumor can be left behind and give rise to a local recurrence, also known as 'second field tumors' (39,40).

The local recurrence rate of laryngeal carcinoma after non-surgical treatment has been reported to be 20-46%, depending on subsite and tumor stage (24,41-44). Surveillance is especially crucial in the first 2-3 years because two-thirds of the local recurrences and persistent or delayed lymph node metastases present in this period (45,46).

Prognosis of patients with a recurrence depends on the time of detection, since late detection is associated with poor survival rates (47-50).

Detection

The detection of recurrent laryngeal carcinoma after (chemo)radiation can be difficult. Symptoms like voice deterioration, pain, dyspnea and dysphagia may be caused by a local recurrence, but can also be the result of post-radiotherapy changes, and are neither very sensitive nor specific (51).

In daily clinical practice standard follow-up consists of physical examination with indirect and fiberoptic laryngoscopy, combined with imaging in selected cases. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound are the anatomic imaging modalities used for detection of recurrent laryngeal carcinoma.

The value of physical examination and anatomic imaging is sometimes limited in the detection of recurrence because of the (chemo)radiation induced changes, such as edema, hyperemia and fibrosis. Conventional imaging depends on soft tissue distortion and contrast enhancement and these are noted in both therapy changes and recurrent tumor. There is growing evidence that these modalities have limitations in their diagnostic accuracy (52-57).

In a survey among head and neck cancer institutions in the Netherlands, 94% of the departments used direct laryngoscopy with biopsies under general anesthesia in case of a suspected recurrence (51). However, in another study we found it often takes several laryngoscopies to detect a recurrence: 31% of the initial laryngoscopies was false-negative (recurrence within 6 months) (51). Furthermore, trauma of multiple biopsies in heavily radiated tissue may initiate superimposed infection, chondritis, failure to heal and further edema (58). On the other hand, some direct laryngoscopies under general anesthesia are performed without showing recurrence and should thus be classified as possibly preventable. In conclusion, there is room for improvement of the diagnostic work-up of these patients.

POSITRON EMISSION TOMOGRAPHY (PET)

General principle

Imaging techniques such as (conventional) MRI, X-ray and CT are primarily used to display anatomy, with changes in size and structure to differentiate between abnormal and normal tissue. PET imaging is a functional modality, providing information of physiological and biochemical activity. Another benefit of PET is that it can image the entire body in a single study, to evaluate the primary tumor, nodal metastases and distant metastases.

PET is based on the administration of a positron emitting pharmaceutical. This type of radio-isotope emits a positron that will travel a distance of a few millimeters. After losing its kinetic energy the positron combines with an electron, converting its mass into energy, and resulting in the formation of two photons or gamma rays with an energy level of 511 keV. This is called annihilation. The photons are simultaneously emitted in opposite directions (under an angle of 180°). A PET camera consists of a ring of detectors placed around the body of the patient. If two photons are detected by detectors on opposite sides within a few nanoseconds, it is assumed that somewhere along the line an event has taken place. This line is referred to as the 'line of response'. By calculation of the crossing of all the lines of response the location of the radiation source can be determined. The current post-image reconstruction resolution of clinical PET systems is 5-7 mm.

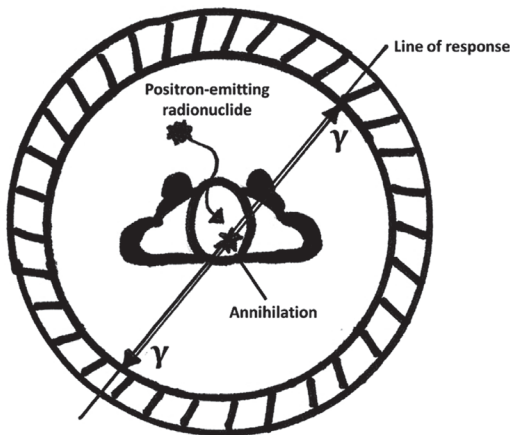


Fig 2. Annihilation, with detection of the two photons (γ radiation) by the PET camera, which surrounds the patient as detector rings.

Tracers

The most frequently used radio-isotope is Fluorine-18 (^{18}F ; $t_{1/2}$ 110 minutes), but also the shorter-lived Carbon-11 (^{11}C), Nitrogen-13 (^{13}N) and Oxygen-15 (^{15}O) as well as the long-lived Zirconium-89 (^{89}Zr) and Iodine-124 (^{124}I) are used for PET scanning. The radio-isotope is linked to a biomolecule, which leads to a PET tracer. For example, labeling of the glucose analogue deoxyglucose with Fluorine-18 results in 2- ^{18}F -fluoro-2-deoxy-D-glucose (18F-FDG)(59). In the oncological field

¹⁸F-FDG is broadly used as PET tracer, since cancer cells have increased glucose metabolism. Analogous to glucose, ¹⁸F-FDG is transported into cells via GLUT-transporters and is converted to ¹⁸F-FDG-6 phosphate. However, unlike glucose-6 phosphate, this is not recognized as a substrate for further processing in the glycolytic pathway and thus accumulates within the cells. Hence, ¹⁸F-FDG-6 phosphate will preferentially accumulate in those cells with high glucose uptake, such as tumor cells. A whole body PET image represents the biodistribution of the glucose analogue in the body. The main drawback of ¹⁸F-FDG as PET tracer for malignancy is the ¹⁸F-FDG uptake in noncancerous tissue, with infection and inflammation as the most frequent culprit of misinterpretation.

¹⁸F-FDG-PET and laryngeal carcinoma

¹⁸F-FDG-PET plays an important growing role in staging, restaging, monitoring treatment and predicting prognosis in patients who have head and neck cancers (60-64). It may be particularly useful to distinguish posttreatment changes from recurrent tumor following radiotherapy (65). For this indication ¹⁸F-FDG-PET with or without CT has proven to be more accurate when compared with conventional imaging modalities (56,66). Sensitivity and specificity of ¹⁸F-FDG PET for detection of residual or recurrent HNSCC were 92-94% and 82-87%, respectively, in meta-analysis (67,68).

However, infection, inflammation, ulceration and necrosis are known postirradiation sequels associated with increased metabolic activity. As a result, PET scans can be falsely reported as tumor-positive and specificity decreases. To avoid false-positive ¹⁸F-FDG accumulation and to enable small residual disease grow to a detectable size, post(chemo)radiation evaluation of the larynx and neck should be done at least 2 months following treatment (62,66,67,69-72). Although specificity after radiotherapy can be disappointing, sensitivity of ¹⁸F-FDG-PET is high.

Innovation in PET is focused on improving the poor quality of anatomic localization (using PET/CT and PET/MRI) and limited spatial resolution, and on the development of more specific tracers. When anatomical data is added, it may be less difficult to distinguish between metabolically active benign versus malignant tissue. In general, the combined use of ¹⁸F-FDG-PET and contrast-enhanced CT provides similar sensitivity but improved specificity and diagnostic confidence, compared with ¹⁸F-FDG-PET alone (73,74). However, a systematic review and meta-analysis did not find a clear benefit of PET/CT over PET alone in head and neck cancer patients following (chemo)radiotherapy or as posttreatment surveillance (67,68,75). Previous PET/CT research has focused on SUV (standardized uptake value) to differentiate between tumor and therapy-induced inflammation. There are no standardized cut-off SUVs to identify residual or recurrent disease in patients with head and neck cancer (76). There are studies indicating that pretreatment ¹⁸F-FDG uptake might be inversely related with disease free survival (77).

SALVAGE TREATMENT

Salvage surgery is, if possible, the only therapeutic option with curative intent for residual or locally recurrent carcinoma after (chemo)radiation. For laryngeal carcinoma salvage surgery mostly consists of total (pharyngo-)laryngectomy which can be combined with uni- or bilateral neck dissection. In selected cases postoperative re-irradiation can be regarded. In certain cases, palliative chemotherapy may be the most appropriate therapy, with variable low response rates.

Locoregional control rate after salvage total laryngectomy for recurrent disease is dependent on the T-stage. The locoregional control rate is around 50-80% for T2 (41,78-82), 50% for T3 (78, 83-85), and 20-30% for T4 tumors (78,86). Salvage surgery after chemoradiation is associated with a significantly lower success rate and higher morbidity than upfront surgery (48,87-92).

Laryngectomy as salvage

Total laryngectomy is widely recognized as one of the surgical procedures with the most impact on patients. Surgical resection compromises voice, swallowing, and the airway and may have a negative impact on the patient's quality of life. Social isolation, job loss, and depression are known sequels. The natural airway is altered by creating a permanent tracheostoma and normal vocal function is eliminated by removing the voice box. Surgical voice restoration using voice prosthesis is the optimal standard for rehabilitation in laryngectomees. The quality of voice is variable (93), but does allow patients to reintegrate into working life.

Various types of open function preservation surgery have been described to avoid total laryngectomy. Partial laryngectomy is mainly performed to allow patients to speak without a stoma, and to minimize the risk of complications. Examples are horizontal and vertical partial laryngectomies or supracricoid laryngectomy (25, 94).

Nevertheless, for most recurrences, partial laryngectomy is no curative option and total laryngectomy will be the only operation of choice. Previous studies showed that depending on the primary tumor site most recurrences are transglottic and largely advanced (rT3-T4) (95). Also, small fields of residual tumor have been found in apparently normal areas of the laryngectomy specimen, indicating the extensiveness of recurrent disease (96,52). Salvage partial laryngectomy seems only suitable in carefully selected patients and indications for this form of surgery vary globally (97).

Salvage laryngectomy is associated with a higher rate of postoperative complications than primary laryngectomy. Problems related to local wound healing, especially the development of pharyngocutaneous fistula, constitute the most common postoperative complication after salvage total laryngectomy (90,98-104).

Neck dissection

The American Academy of Otolaryngology Head and Neck Surgery established a system for classifying cervical lymph nodes into different surgical zones, based on their anatomic locations (105). This system is designed to improve communication regarding the location of abnormal nodes and to ensure reproducible lymph node dissections. Lymph nodes in the neck have been

divided into 6 levels: level I, submandibular triangle; level II, upper jugular; level III, middle jugular; level IV, lower jugular; level V, posterior triangle, and level VI, pre/para- laryngeal and -tracheal lymph nodes.

Pre-operative ultrasound is the most valuable technique to detect and localize lymph node metastases, especially if combined with cytological aspiration (106). However, its value in the clinically negative neck is limited. CT, MR and PET imaging are also used to detect lymph node metastases. In meta-analysis PET has good performance compared to conventional diagnostic tests, but still does not detect disease in half of the patients with metastasis and cN0 (107,108). PET has not shown consistent utility in evaluating small subcentimeter lymph nodes because of its innate limitations in camera resolution, while 40% of metastatic cervical lymph nodes measure less than 7 mm in diameter (109,110).

Unfortunately, posttreatment ultrasound-guided-fine needle aspiration cytology lacked specificity in patients after chemoradiation in a previous study (111). PET/CT is currently advocated as the posttreatment imaging modality of choice, but due to the false-negative rate its use in clinical practice is under debate: some studies find the false-negative rate too high to warrant deferring neck dissection (110,112,113), whereas others find no survival benefit for planned neck dissection as compared to selection for neck dissection by PET/CT (114).

The status of lymph nodes in the neck is a major determinant of the outcome in patients with local recurrence. However, proper management of the neck remains a therapeutic dilemma. There is no consensus over whether or not and how to perform neck treatment in patients with recurrent laryngeal carcinoma.

There is general agreement that patients with less than complete response in the neck after (chemo)radiotherapy should undergo neck dissection to eliminate potential residual viable tumor cells in the nodes (115,116). It has also been accepted that patients with complete response of N1 disease do not require neck dissection (117,118). The controversy is principally centered over whether a clinical complete response predicts eradication of N2-3 disease (113). A review showed that the overall rate of occult lymph node metastases in patients undergoing salvage surgery for recurrent laryngeal carcinoma ranged from 7.5-12% (119).

The type of neck dissection is another area of controversy. There are three main categories of neck dissection (120). Radical neck dissection is the standard basic procedure for cervical lymphadenectomy which includes removal of lymph nodes from levels I to V, with removal of the sternocleidomastoid muscle, the spinal accessory nerve, and the internal jugular vein. Modified radical neck dissection involves removal of lymph nodes from levels I to V (as in radical neck dissection), but with the preservation of at least 1 of the nonlymphatic structures (i.e., sternocleidomastoid muscle, spinal accessory nerve, and/or internal jugular vein). The term selective neck dissection is applied when one or more lymph node level(s) is preserved. There are several types of the selective neck dissection, some of which have traditionally been given specific names (eg, lateral, supraomohyoid, extended supraomohyoid, posterior or central). However, since 2001 it was determined to exclude these 'named' selective neck dissections based

on the increased number of variations (121). To facilitate the standardization and referencing of these procedures the levels are described, with the addition of sublevels into the classification (IA: submental nodes, IB: submandibular nodes, IIA and IIB: upper jugular nodes (anterior caudal and posterocranial from spinal accessory nerve), VA: spinal accessory nodes and VB: transverse cervical and supraclavicular nodes). In some selected cases, a superselective or nidusectomy seems feasible (116).

In primary laryngeal carcinoma, most regional lymph node metastases are in the upper and middle jugular chain of nodes (level II and III) (122). It seems therefore, and this was confirmed by previous studies, not necessary to perform a comprehensive neck dissection in patients with limited regional recurrence (111, 116).

In conclusion, since detection of regional recurrence after non-surgical treatment remains difficult, management of the neck constitutes a dilemma in patients with proven local recurrence.

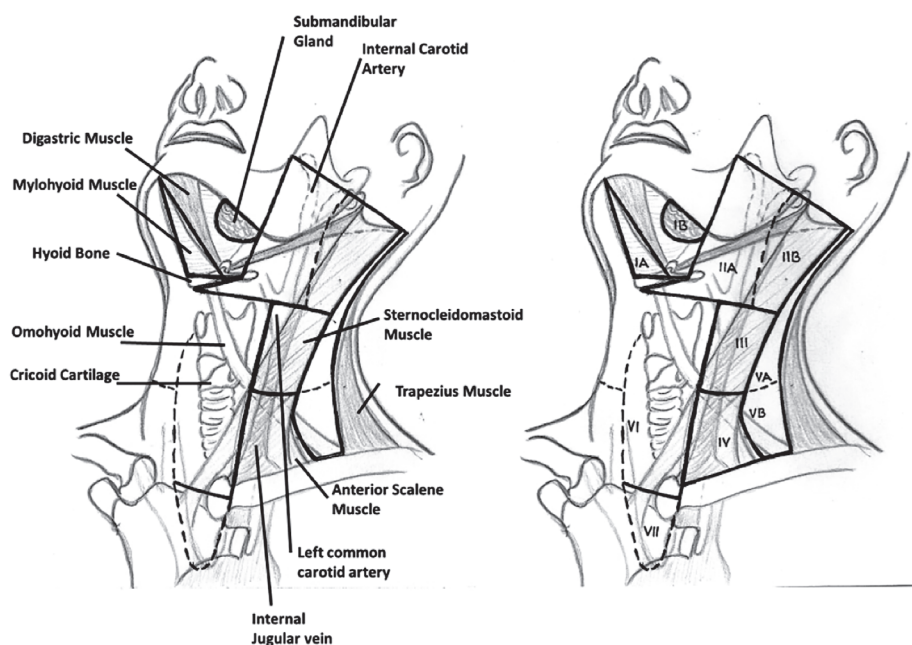


Fig 3. Lymph node levels of the neck in relation to important structures of the neck, used as landmarks for the extension of lymph node dissections. Adapted from reference 123.

COST EFFECTIVENESS

Cost (-effectiveness) analysis (C(E)A) has proven value and is widely used to assist in health care decision making (124). The increasingly competitive medical landscape demands that current and future costs as well as quality of care and patient perspective become central to health care

decision making (125). Anywhere that a determination of the value of a health intervention would be useful is a potential arena for the application of C(E)A.

Cost-effectiveness analysis, compares different costs between treatments in relation to outcomes (effects). Cost-minimization analysis quantifies medical costs without analyzing the effectiveness outcomes, and is used when differences in outcome are not expected.

In the development of new guidelines the government and health insurances promote the importance of cost-effectiveness of expensive medical technologies. A diagnostic imaging technique is considered effective if it provides more accurate data than existing modalities, improves patient management and contributes to better impact on health. Secondly, there is an increasing aspiration to provide this at reasonable costs. When two diagnostic or treatment strategies are compared, a cost (-effectiveness) analysis can be performed in which the potential health benefits and cost consequences of the new intervention are compared against a reference script (diagnostic or treatment used in best practice). The effect, or primary outcome event, can be diagnosing a patient with a disease, longer survival, or a futile intervention. Costs can be compared between groups. Medical costs concern direct medical costs and direct non-medical costs (for example costs for the patient to travel to the hospital and loss of productivity). Relevant costs here are related to hospitalization, operation and PET scan. By performing sensitivity analysis the impact of the most influential input parameters on the costs and outcomes can be examined.

AIMS AND OUTLINE OF THE THESIS

As (chemo)radiotherapy is currently the most often used treatment for primary laryngeal carcinoma, the role of surgery is evolving from primary surgery towards salvage surgery. Salvage surgery is known to result in a better survival rate when performed timely, but the detection of a local recurrence can be difficult. Therefore, reliable diagnostics to detect the residual or recurrent tumor as early as possible are mandatory. The current standard to detect local recurrence, direct laryngoscopy (with biopsies) under general anesthesia, has several disadvantages. As a result of radiation sequelae, it can be difficult to distinguish scar tissue from tumor, with false-negative biopsies as a consequence. Previous research indicates that 18F-FDG-PET might be reliable enough to exclude the presence of tumor.

When residual or recurrent local tumor is proven, salvage surgery should be considered. Salvage laryngectomy means function loss and postoperative complications and survival is poor. A careful selection should therefore be made, with consideration towards the extent of surgery.

The aims of this thesis was to investigate the role of 18F-FDG-PET in the detection of local recurrent laryngeal carcinoma after (chemo)radiotherapy (**Chapters 2-5**) and to evaluate the outcome of salvage surgery (**Chapters 6-8**).

The role of 18F-FDG-PET in the detection of locally recurrent laryngeal carcinoma

In **Chapter 2** the observer variability in reporting of 18F-FDG-PET to detect recurrent laryngeal cancer, is studied between 11 observers from different centers. Observer variation is the Achilles'

heel of visual imaging interpretation (126). Purpose of this study is to give a nation-wide impression of the accuracy (and its range) of 18F-FDG-PET for this indication in daily clinical practice. At the same time, it was used as a training set for the following RELAPS study.

In **Chapter 3** we describe the design of a randomized controlled multicenter trial (RELAPS: REcurrent Laryngeal carcinoma after radiotherapy, PET Study). The study is conducted to improve the yield of direct laryngoscopy by setting its indication via PET, randomizing patients either to direct laryngoscopy with biopsies under general anesthesia (conventional strategy) or to 18F-FDG PET only followed by direct laryngoscopy with biopsies under general anesthesia if PET was assessed positive or equivocal for the presence of local disease (PET-based strategy). The assessment and distribution of new technologies is a complex process. There may be either a low level of acceptance of new technologies in the medical community, or, more frequently, overuse. The major benefit of randomization lies in the creation of groups that are similar with respect to all known and unknown prognostic factors allowing an unbiased comparison of different strategies. Another benefit of using a randomized controlled trial is that not only the accuracy of PET is investigated, but an entire strategy. This strategy consists of a diagnostic and treatment combination, allowing to evaluate the total effect on patient outcome.

In **Chapter 4** the results of the RELAPS trial are discussed. The clinical significance of the PET-based diagnostic strategy is evaluated, in relation to the number of futile indications for direct laryngoscopy under general anesthesia. Also, the safety of this strategy and accuracy of PET is studied. Safety is investigated by the percentage of patients with local recurrence undergoing laryngectomy and the percentage of positive margins in each diagnostic strategy arm.

In **Chapter 5** a quantification of medical costs is presented. The mean medical costs of the PET based strategy versus the conventional strategy are studied. Costs are subdivided for diagnostic, treatment and follow-up phase. A sensitivity analysis was performed to examine the impact of different input parameters.

Salvage laryngectomy and neck dissection for recurrent laryngeal carcinoma

In **Chapter 6** the recurrence patterns of hypopharyngeal and laryngeal carcinoma after chemoradiation are investigated. Predictors for salvage laryngectomy and lymph node dissections for locoregional recurrence and outcome are described. In addition, an overview of the outcome in previous studies is presented.

In **Chapter 7** we investigate the functional and oncologic outcome of salvage laryngectomy after previous radiotherapy. Secondary, management of the neck in combination with laryngectomy is discussed and prognosticators are evaluated.

In **Chapter 8** we describe the histopathologic results of paratracheal lymph node dissections that were performed during laryngectomy after previous radiotherapy. Furthermore, the relation between postoperative complications and the extension of the paratracheal dissection is investigated.

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